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| EXAMINER | |
|---|---|
| WHITEMAN, BRIAN A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | // |

DATE MAILED: 12/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/927,091 | KILLARY ET AL. | |
| | Examiner | Art Unit | |
| | Brian Whiteman | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-100* is/are pending in the application.

4a) Of the above claim(s) *18-23,34-43 and 45-96* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-17 and 97-100* is/are rejected.

7)☒ Claim(s) *1-6,24-33,44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### Non-Final Rejection

Claims 1-100 are pending examination.

### *Election/Restrictions*

Applicant's election without traverse of Group I (1-17, 24-33, 44, 97-100, SEQ ID NOs: 1 and 3) in Paper No. 10 is acknowledged.

Claims 18-23, 34-43, 45-96 and SEQ ID NO: 2 in claims 1-6, 24, and 44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 10.

### *Claim Objections*

Claims 1-6 are objected to because of the following informalities: the phrase "an amino acid sequence of SEQ ID NO: 1" is improper because there is only one amino acid sequence for SEQ ID NO: 1. Suggest amending the phrase to recite -- the amino acid sequence of SEQ ID NO: 1 --. Appropriate correction is required.

Claim 97 is objected to because of the following informalities: The phrase "A isolated and purified nucleic acid" is grammatically incorrect. Suggest amending the claim to recite -- An isolated and purified nucleic acid --.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 7-17 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

Claims 7-17, as written, do not sufficiently distinguish over nucleic acids, as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified" as taught by page [20] of specification. See MPEP 2105.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-17 and 97-100 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid comprising about 3,500 contiguous base pairs of SEQ ID NO: 3 or an isolated nucleic acid that over its entire length hybridizes to a DNA segment of 3,826 bases of SEQ ID NO: 3, does not reasonably provide enablement for an isolated nucleic acid of about 15 to about 5,000 base pairs comprising at least

15 contiguous base pairs of SEQ ID NO: 3 or an isolated nucleic acid that hybridizes under high stringency conditions to a DNA segment comprising at least 15 bases of SEQ ID NO: 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The invention is directed to a nucleic acid of about 15 to 5000 base pairs comprising from about 15 contiguous base pairs of SEQ ID NO: 3 or the complement thereof. The invention is in the field of making and using nucleic acid sequences.

Claims 7-17 recite a nucleic acid of about 15 to 5000 base pairs comprising from about 15 contiguous base pairs of SEQ ID NO: 3 or the complement thereof. The specification contemplates that the nucleic acid can encode a protein that may have tumor suppressor activity. However, other than a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 1 or the nucleic acid sequence of SEQ ID NO: 3, the specification fails to disclose any other nucleic acid with tumor suppressor activity. Furthermore, the specification provides no guidance as to which (if any) of the nucleotides or amino acids may be changed while tumor suppressor activity is retained. The total number of 475 amino acid peptides (amino acid encoded by SEQ ID NO: 3) is $1.07 \times 10^{66}$. The number of single amino acid substitutions is 9,025. The number of two amino acid substitutions is over 80,000,000. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these

changes is largely unpredictable as to which ones have a significant effect versus not. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over polypeptides of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Baker et al., Science, 294:pages 93-96, 2001); Attwood, T (*Science*, vol. 290, no. 5491, pp. 471-473, 2000); Gerhold et al., (*BioEssays*, vol. 18, no. 12, pp. 973-981, 1996); Russell et al., *Journal of Molecular Biology*, vol. 244, pp 332-350, 1994); and Wells et al., *Journal of Leukocyte Biology*, vol. 61, no. 5, pp. 545-550, 1997). Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain tumor suppressor activity, and the fact that the relationship between the sequence of a peptide and its tertiary structure are not well understood and are not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al (ed.), Birkhauser. Boston, MA, pp. 433 and 492-495), it would require undue experimentation for one skilled in the art to arrive at other peptides that have tumor suppressor activity. In addition, in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 U.S.C. 112, first paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for the determination of other genetic sequences that are embraced by the claim. This is the case here. In other words, since it

would require undue experimentation to identify other peptides that have tumor suppressor activity, it certainty would require undue experimentation to make their corresponding nucleic acid of about 15 to about 5000 base pairs comprising from about 15 contiguous base pairs of SEQ ID NO: 3 or the complement thereof, and, therefore any nucleotide sequence that may encode a polypeptide sequence that might have tumor suppressor activity is not enabled by the claimed embodiment.

The specification discloses and the claims 97-100 recite an isolated and purified nucleic acid that hybridizes under high stringency conditions to a DNA segment comprising about 15 to 3826 bases of SEQ ID NO: 3 as well as methods of using the nucleic acids to detect CAR-1. However, the state of the art as exemplified by Wallace et al., (Methods Enzymol. 152:432-443, 1987) and Sambrook et al., Molecular Cloning, A Laboratory Manual, Second Edition, 1989, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, p. 11.47) is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Furthermore, a database search was done for the nucleotide sequences set forth in SEQ ID NO: 3, which suggest that some of the probes encompassed by the claims would not preferentially hybridize to DNA of SEQ ID NO: 3 and not to non- SEQ ID NO: 3 nucleic acid so as to detect SEQ ID NO: 3. See Wang (US 2002/0198371, SEQ ID NO: 100,265 and Penn et al., US 2002/0048763, SEQ ID NO: 7,231). There are no working examples and there is no suggestion as to what the target sites in SEQ ID NO: 3 are or what modifications can be made to the sequence or the hybridization conditions while retaining the ability to detect SEQ ID NO: 3. In addition, claims 97-100 recite one limitation on the nucleic acid. The structural limitations is 1) that the DNA segment comprising

about 15 to 3826 bases of SEQ ID NO: 3. Since the nucleotide sequence mentioned merely comprises at least 15 bases from a nucleotide sequence of SEQ ID NO: 3, it encompasses any random sequence of any length as long as it has a stretch of at least 15 bases that is the same as in SEQ ID NO: 3. Furthermore, since there is no limitation that claimed nucleic acid hybridizes to the nucleotides that is the same as in SEQ ID NO: 3, claim 97 embraces any nucleic acid that is 15 to 3826 bases in length. In view of this, the empirical and unpredictable nature of the art, the lack of guidance with respect to appropriate modifications and the lack of guidance as to how to use probes within the scope of the claims to detect SEQ ID NO: 3, the specification does not teach one skilled in the art how to successfully use probes of the claimed scope of without undue experimentation.

In conclusion, in view of the In Re Wands Factors, the as-filed specification and claims coupled with the art of record at the time the invention was made do not provide sufficient guidance and/or evidence to reasonably enable one skilled in the art to practice the full breadth of the claimed invention. One would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the application's disclosure. Furthermore, the specification does not provide sufficient guidance in view of the art of record and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (Fed. Cir. 1991) for making and/or using a nucleic acid of about 15 to 5,000 base pairs comprising from about 15 or more contiguous base pairs of SEQ ID NO: 3 and/or an isolated nucleic acid that hybridizes to a DNA segment comprising about 15 to 3826 bases of SEQ ID NO: 3.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 7-15 and 97-100 are rejected under 35 U.S.C. 102(a) as being anticipated by Waterson (GenBank Accession No. AC022262, US National Library of Medicine, Bethesda, MD, July 2000, accessed by PTO on 10/23/03). Waterson teaches a nucleotide sequences that is 100% identical to 1,479-2,093 and 2,095-3,807 of applicants' SEQ ID NO: 3.

Claims 7-14 and 97-100 are rejected under 35 U.S.C. 102(e) as being anticipated by Wang (US 2002/0198371). Wang teaches a nucleotide sequences that is 100% identical to 2345-2921 of applicants' SEQ ID NO: 3 (page 5, SEQ ID NO: 100,265).

Claims 7-13 and 97-100 are rejected under 35 U.S.C. 102(e) as being anticipated by Penn et al., (US 2002/0048763). Penn teaches a nucleotide sequence that is 100% identical to 1,602-2,093 of applicants' SEQ ID NO: 3 (SEQ ID NO: 7231). Penn teaches a nucleotide sequence that is 100% identical to 1,643-2,073 of applicants' SEQ ID NO: 3 (SEQ ID NO: 23,962).

***Conclusion***

Claims 1, 24, and 44 are objected to for reciting non-elected embodiment (SEQ ID NO: 2).

Claims 2-6 and 25-33 are objected to for depending on a claim that recites non-elected embodiment.

Claims 1-6, 24-33, and 44 would be allowable if the independent claims (claims 1, 24 and 44) were amended to delete the non-elected embodiment (SEQ ID NO: 2).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

Brian Whiteman
Patent Examiner, Group 1635

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER